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ABSTRACT

A classification of natal influences is proposed with a model of their operation. Natal influences affect maternal capacity, maternal load, and maternal efficiency. Since maternal load is increased in twin pregnancy, results of twin studies must be generalized with caution. The method of co-twin control is exemplified by examination of a small sample. The results of the intrapair analysis imply that current formulations of hereditary and environmental contributions to phenotypic variation are inadequate to account for observed intrapair differences. Two alternative, though nonexclusive, interpretations of intrapair variation are suggested. The first interpretation stresses the role of complex maternal-fetal-environmental interactions, and the second, a "genetic indetermination" which derives, in part, from the information characteristics of the genes. (Author)

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# NATAL INFLUENCES AND TWIN DIFFERENCES

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# Natal Influences and Twin Differences

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## Abstract

A classification of natal influences is proposed with a model of their operation. Natal influences affect maternal capacity, maternal load, and maternal efficiency. Since maternal load is increased in twin pregnancy, results of twin studies must be generalized with caution. The method of co-twin control is exemplified by examination of a small sample. The results of the intrapair analysis imply that current formulations of hereditary and environmental contributions to phenotypic variation are inadequate to account for observed intrapair differences. Two alternative, though nonexclusive, interpretations of intrapair variation are suggested. The first interpretation stresses the role of complex maternal-fetal-environmental interactions, and the second, a "genetic indetermination" which derives, in part, from the information characteristics of the genome.

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# Natal Influences and Twin Differences[1]

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## A. Introduction

In the following paper, a typology of natal influences is described, a mechanism of natal influences suggested, and some of the limitations of twin studies discussed. The application of twin technique to the examination of natal influences is illustrated with a small sample. Certain empirical claims, such as the relation between birth weight and intelligence, are reexamined, and a mechanism of optimum gestation is proposed. The results of the intrapair evaluation suggest the inadequacy of current formulations of hereditary and environmental contributions to neonatal phenotypic variation. Two alternative interpretations are proposed. The first interpretation stresses the role of complex maternal-fetal-environmental interactions, and the second, a "genetic indetermination" related, in part, to the information characteristics of the genome.

### 1. Co-twin Control

One of the major problems of reproductive causality is the relative contribution of genetic and natal environmental factors to later behavior. In studies of single children, particularly when samples are heterogeneous, genetic and environmental factors are often confounded. One technique which exercises effective control over genetic variation derives from variations of pre- and paranatal factors which affect members of identical twin sets. Since variation due to genetic sources is equivalent for identical twins, phenotypic variation

may be assumed to express variation due to natal environmental differences or their interaction with genetic determinants (11, 14, 17, 26). The method is the natal analogue of the post-natal study of identical twins subject to different rearing conditions.

## 2. Birth Weight and Intellectual Differences

One of the primary concerns of co-twin studies addressed to the long-term effects of pre- and paranatal factors has been the relation of birth weight to later intelligence. Co-twin studies of this problem usually postulate some nutritional inadequacy (1), intrauterine insufficiency (5), or circulatory deficit (15, 24), which may affect prenatal development quantitatively and qualitatively. Birth weight differences between monozygotic twins are assumed to vary with the operation of such factors. Relative to the larger twin, the smaller twin is viewed as "prenatally disadvantaged."

The postulate of nutritional, intrauterine, or circulatory insufficiency suggests some correspondence between the degree of weight difference and intelligence difference. Nevertheless, with two exceptions (15, 29), co-twin studies have simply dichotomized between heavier and lighter twin members. Twins with weight differences as small as 10 grams have been pooled with twins with weight differences as large as 2,000 grams (24, 28). When dichotomized in this way, significant intellectual differences emerge between heavier and lighter monozygotic twins, but not dizygotic twins (5, 15). In fact, the average IQ difference between heavier and lighter monozygotic twins has been more than five points or roughly equivalent to the average IQ difference of identical twins reared together.

Although the postulate of nutritional, intrauterine, or circulatory deficit largely derives from the investigations of the German physiologist Shantz, reviewed by Price (23), Shantz himself believed that the smaller twin was usually advantaged. Unfortunately Price does not summarize Shantz's rationale for this assertion. However, one may speculate that the smaller member of a twin set may be less disadvantaged since his demands for oxygen, nutrients, etc. are proportionately smaller than his larger co-twin.

## 3. A Typology of Natal Influences

Numerous other natal factors associated with intelligence have been implicated in retrospective studies (10, 11, 12, 18, 19). In a general way, these factors may be classed as prenatal or paranatal, environmental or organismic, and specific or general. These factors may be projected in a two by two by two table to summarize some of the variables associated with intelligence and adaptability (Table 1). Prenatal factors affect the conceptus prior to birth, and

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Insert Table 1 about here

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paranatal factors, at or around the time of birth. Environmental factors derive from external manipulations or treatments while organismic factors describe maternal-fetal characteristics. Specific factors are associated with a single member of a set, and general factors are common to members of a set.

Natal studies with co-twin control necessarily involve the identification of specific factors which differentially affect members of the twin set. Within sets, specific factors may be concordant or nonconcordant. Both members of a twin set may present in a cephalic or breech position, or one with cephalic and

one with breech position, etc. When a specific factor is largely concordant within sets, intrapair difference attributable to that factor is reduced. Hence, a requirement of intrapair analysis is a sufficient number of nonconcordant subjects within sets to obtain the necessary sensitivity to statistical test. However, this requirement does not justify the elimination of concordant sets. The expectation of no difference within pairs when concordant is the corollary of the expectation of difference within pairs when nonconcordant. Deletion of concordant sets in co-twin analyses, such as twin sets with the same weight or intelligence (24), discards useful information.

## 4. Mechanism of Natal Factors

An examination of Table 1 reveals the diversity of natal factors. Different factors possess distinct modes of action with different consequences for the fetus. The mode of action of these factors and their significance for the fetus may be summarized in terms of three interdependent concepts, maternal capacity, maternal load, and maternal efficiency. Maternal capacity describes the maternal ability to provide various nutrients, eliminate metabolites, and "buffer" the fetus against various toxic substances. Maternal load is the complement to maternal capacity. It summarizes the demands placed upon the maternal system for nutrients, elimination of metabolites, and neutralization of toxic substances. Maternal efficiency characterizes the maternal response to maternal load. This response, in turn, depends upon maternal capacity:

$$\text{Maternal efficiency} = \frac{\text{Maternal capacity}}{\text{Maternal load}} \quad .$$

Poor maternal efficiency may derive either through low maternal capacity or through high maternal load. In general, as maternal efficiency decreases,

the probability of fetal damage increases. Selected natal factors which provide an index of maternal capacity, maternal load, and maternal efficiency are classified in Table 2.

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Insert Table 2 about here

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5. Limitations of Twin Method

Co-twin differences attributable to natal factors must be interpreted with considerable caution. Twins are not representative of the general population, and factors may operate in twin pregnancies which are absent or minimal in single pregnancies (9, 13, 19, 21).

During multiple pregnancies, utero-placental circulation is dramatically slowed. Morris et al. (20) demonstrated that average clearance time of radiosodium from the utero-placental pool required more than 60 minutes in twin pregnancies in contrast to 4 minutes in single pregnancies. As circulation is less efficient, supply of oxygen and nutrients as well as elimination of metabolites and toxic substances may be considerably impaired. Monozygotic and dizygotic twins at all stages of intrauterine gestation weigh less and are shorter than singletons. Newman (22), Eastman (8), and others (7) argue this weight and height disadvantage derives from the failure of the mother to provide adequate nutrients. Oxygen demands are approximately doubled in twin pregnancies and, hence, periods of minimal and acute anoxia are more probable (21). Moreover, preeclampsia, eclampsia, toxemia, and other complications which implicate maternal inadequacies of physiological response are more frequent, particularly during the last trimester of pregnancy (19).

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Since the increased load of twin pregnancy appears to reduce maternal efficiency, pre- and paranatal insults which are inconsequential in single pregnancies may generate relatively potent effects. That is, one may expect the role of various pre- and paranatal insults to be exacerbated in multiple pregnancies.

### 6. Natal Influences among a Sample of Identical Twins

The application of the typology of natal influences may be illustrated through evaluation of intra- and interpair intellectual differences in a sample of identical twins. Such evaluation provides a basis for examination of the limitations of twin technique and for scrutiny of the empirical match between selected natal influences and their proposed mechanism.

## B. Method

### 1. Subjects

Three constraints were placed on sample selection to reduce extraneous variation or otherwise increase co-twin variation due to natal factors. First, twin sets were derived from a relatively homogeneous middle class population. Second, twin sets with a member who manifested positive evidence of neurological damage were excluded. Although neurological damage may derive from traumatic pre- or paranatal factors such damage may exaggerate, confound, or mask group effects. Third, twin sets were selected from an age range between 10 and 90 months with the expectation that effects due to natal differences would be more marked at earlier than later ages.

A population of identical twins within the appropriate age range were identified in the Champaign-Urbana, Illinois area through the cooperation

of the Twin Club and local pediatricians. Although an effort was made to evaluate the entire population, five families were not located and one family refused cooperation. Nineteen sets were examined. One set, however, was not testable, and members of two sets had histories of previous special education intervention. When these sets were eliminated the reduced sample was 16 sets (N = 32). Confirmation of zygosity was obtained through placental examination, skin graft, serological, dermatoglyphic, or physical concordance.

## 2. Procedure

Twin members over two years old (N = 12 sets) were randomly assigned to two examiners and administered the Stanford-Binet Form L-M Intelligence Test in parallel rooms. Twin members under two years old (N = 4 sets) were administered the Bayley Mental Scale. The procedure for administration of this test was rendered flexible due to occasional fatigue or separation protest. Sets were either tested together with alternate items and/or tested in succession.

Concurrent with the administration of the Stanford-Binet or after the administration of the Bayley, mothers were interviewed about their prenatal and birth histories. The interview included questions about prescriptions, drugs, dysfunctions, diet, labor, anesthetics, and a set of more specific items. The average interview was about 40 minutes in duration. The obstetricians who attended delivery of the twin sets were provided parallel forms to supplement or correct information obtained through maternal interview. Fifteen physicians replied. When maternal and obstetric reports differed, the information obtained from the obstetric report was coded for statistical analysis.

## C. Intrapair Evaluation

### 1. Results

Information about six specific paranatal factors was obtained from obstetric records. The factors included birth order, birth weight, presentation, neonatal Apgar, use of forceps, and period of umbilical separation. Each factor was scaled to correspond to clinical difficulty or the severity of stress presumptively related to various levels of that factor. Cephalic presentations were rated "0"; breech presentations, "1"; and transverse presentations, "2." Neonatal Apgar was assigned to three classes, "1," poor (Apgar 4 or less); "2," fair (Apgar 5-7); and "3" good condition (Apgar 8-10). No forceps was rated "0"; low forceps, "1"; midforceps, "2"; and high forceps, "3." Umbilical separation was rated "1" when the cord was clamped immediately after delivery; "2," after pulsations of the cord had ceased; and "3," after separation of the placenta (30). All sets were nonconcordant for birth order and birth weight, six sets for presentation, four sets for neonatal Apgar, two sets for use of forceps, and no sets for umbilical separation. Since no variation for the last factor occurred it was excluded from intrapair analysis.

Correlational analyses between factor and intellectual difference scores were calculated for each factor. Difference scores for birth weight and intelligence were treated as a ratio of difference between heavy and lighter members of a twin set by the formula:

$$R = \frac{x_h - x_l}{x_h + x_l}$$

where R is the ratio of difference to total score, $x_h$, the value of the heavier twin, and $x_l$, the value of the lighter twin. Adjustment of sign (plus

or minus) for the specific factor difference scores which remained was applied when appropriate. The dependent variable for all correlations was the ratio of intellectual difference (Table 3).

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Insert Table 3 about here

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## 2. Discussion

No significant relationship was obtained between intrapair differences for specific paranatal factors and intrapair differences in intelligence. Nonconcordance for presentation, neonatal Apgar, and use of forceps was relatively infrequent, and results for these factors are not reliable. However, nonconcordance for birth order and birth weight was sufficiently large to provide a reasonable test of their effect.

Difference scores for birth order approached significance with a 3.82 IQ advantage for the second born. This difference may derive from the latter's "easier" birth. Since dilation of the cervix and uterus is relatively complete for the second born, intracerebral pressure with its attendant complications may be reduced. This result appears to agree with that of Koch (16), but remains inconsistent with the obstetric observation that complications of delivery and neonatal damage are more frequent with the second born (2). As Koch suggests, this result may derive through a sample bias associated with differential selection, i.e., only the more "fit" second-born twin members survive.

The failure to replicate the association between birth weight and intellectual differences among identical twins introduces methodological and interpretative problems. The postulate of nutritional, intrauterine, or circulatory

insufficiency suggests some relation between the degree of weight difference and intellectual difference. Evaluation of group mean differences characteristic of earlier studies is only suggestive of this relationship. That is, not only group mean differences are anticipated, but some systematic intrapair covariation between weight and intellectual advantage. In fact, the insufficiency postulates suggest that group mean differences derive from this covariation.

To test this expectation, the primary data from five recent studies (1, 5, 15, 24, 29) which report group mean intellectual differences between heavier and lighter twins were subject to a correlational analysis. The correlational procedure provides a measure of intrapair covariation between the magnitude of weight and intellectual differences unconfounded with the group mean differences already reported in the literature. The number of subjects and results of correlational analysis are reported in Table 4.

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Insert Table 4 about here

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One study suggests a positive relation (15), two suggest no relation, (24, 29), and two suggest a negative relation (1, 5). The direction of relation remains the same when the ratio of weight difference is regressed against the ratio of intellectual difference. Moreover, when subjects are pooled and partitioned by midtwin weight, no significant linear or curvilinear association occurs between intrapair weight and intellectual difference (27). Thus, the group mean differences between heavier and lighter twins reported in the literature do not derive from systematic intrapair covariation of weight and intellectual difference. That is, whether the weight difference between a pair of twins is 10 grams or 2000 grams is independent of the magnitude of IQ difference

between the twins. This conclusion is consistent with the results of the present investigation and inconsistent with the various insufficiency postulates which suggest some correspondence between the magnitude of weight and intellectual difference. The group mean differences reported in earlier studies remain problematic.

## D. Interpair Evaluation

### 1. Results

A total of 15 pre- and paranatal factors were assessed for interpair differences. Seven of the 15 factors were the general, endogenous, prenatal type: (1) maternal age at the time of twin birth; (2) the frequency of prior known miscarriages and stillbirths; (3) prior parity; (4) the approximate maternal weight at conception; (5) maternal weight gain or loss with twin pregnancy; (6) maternal dysfunctions, such as diabetes, hyper- and hypothyroidism, anemia, etc., weighted for degree of dysfunction on a three-point scale (1-3), mild, moderate or severe; and (7) maternal oedema adjusted for degree of oedema (1-3) for extremities, feet, hands, and face. Two factors were the general, exogenous, prenatal type: (8) frequency of diagnostic X-ray; and (9) number of prescriptions administered with pregnancy. Four factors were the general endogenous, paranatal type: (10) neonatal maturity classed in one of seven categories (1-7), 28 weeks or less, 29 to 32 weeks, 33 to 36 weeks, 37 to 39 weeks, full term, 1 to 2 weeks postmature, 3 or more weeks postmature; (11) length of labor assigned to one of three classes (1-3), less than 3 hours, 3 to 23 hours, and 24 hours or more; (12) mean neonatal Apgar, the average value for the twin pair; and (13) mean birth weight. Two factors were the general, paranatal, exogenous type: (14) anesthetic assigned to one of five

categories (0-4), none, 100 mg or less, 100 to 200 mg, or 200 mg or more, analgesic or anesthetic administered at the time of labor; and (15) mean umbilical separation. In addition, two nonnatal variables, the subject's sex and chronological age were included in the analysis. The dependent variable was the average IQ for the individual members of each twin set.

The means, standard deviations, and correlations of natal factors, sex, and chronological age with midtwin intelligence are provided in Table 5.

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Insert Table 5 about here

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Exposure to ionizing radiation during pregnancy and neonatal maturity were significantly inversely correlated with IQ. The chronological age of the subject at the time of IQ evaluation was significantly positively correlated with IQ.

## 2. Discussion

### a. Pre- and Paranatal Factors

Although the majority of natal factors failed to obtain significance, the direction of effect for such prenatal factors as maternal age, previous stillbirths, weight gain, dysfunction, and the clinical administration of prescriptions was in the direction expected from the postulates of maternal load, capacity, and efficiency. With the exception of neonatal maturity and birth weight discussed below, the direction of effect for paranatal factors was far less consistent. Prenatal factors typically operate for the duration of pregnancy; paranatal factors, again with the exception of neonatal maturity and birth weight, operate for a relatively brief period. Hence, the effect of prenatal factors

is less subject to the vicissitudes of relatively transient situational factors such as maternal state, obstetric skill, etc.

b. Maternal Efficiency and Intelligence

As suggested earlier, twin pregnancies appear to place an increased burden on maternal physiological capacities. In twin pregnancies, particularly during the last trimester of pregnancy, maternal efficiency is reduced. Mature twins, late in pregnancy, are more likely to experience a less advantaged uterine environment with reduction of necessary oxygen and nutrients and increase of toxic substances. Since the developing fetal brain is particularly sensitive to anoxia, nutrient deprivation, and toxicity, an inverse relation between intelligence and midtwin weight is expected. Prematurity, common to twin births, may provide an adaptation to limited maternal exchange capacity. In view of these considerations, the assertion, "The bigger the baby, the better (24)," and similar conclusions seem exaggerated. More likely, with twin births, as Koch (16) maintains, there is some optimum maturity.

The optimum maturity probably expresses in part some compromise between maternal load and maternal capacity. Even a small load may exceed maternal physiological limits if capacity is poor with correlative injury to the fetus. In an ideal system, when:

Maternal load = Maternal capacity

for some nontrivial time duration, the birth reflex is elicited and potential damage to the fetus or mother, minimized. Selected studies of singletons (6) reviewed by Caputo and Mandell (4) suggest "small for dates" neonates (prematurity by gestational age) are relatively disadvantaged while "small for

weights" neonates (prematurity by weight) are not. If the prematurity of the small for weights and small for dates neonates derive from poor maternal efficiency, the small for dates neonate experiences this environment for a longer duration than the small for weights neonate. Thus, certain obstetric practices, such as the administration of muscle relaxants to delay pregnancy to full-term gestational maturity, may be ill-advised. This would appear particularly true with twin pregnancy.

c. Twin Catch-up

The consequences for intelligence of increased maternal load are likely to diminish with postnatal development. Experimental studies of teratological agents suggest that cell groups characterized by rapid development are more vulnerable to the deleterious effects of biochemical imbalance. Since the development of the cortex is, in a relative sense, less complete at birth than the development of lower brain centers, verbal and interpretative functions associated with the cortex may be expected to be less impaired than sensory-motor functions associated with lower brain centers. Insofar as sensory-motor tasks are characteristic of intelligence tests for younger subjects and verbal and interpretative tasks for older subjects, the effect of increased maternal load on IQ may be anticipated to be larger with younger subjects.

## E. Theoretical Implications

As the largely negative results of the intrapair analysis suggest, the determinants of individual differences between identical twins are potentially complex. The poor fit between the data and the expectation that differences in natal conditions account for intraindividual twin differences may be briefly illustrated by reference to two cases.

Twin set 11: The twins Q. and R. were discordant for at least four natal factors. Q. was delivered with cephalic presentation, possessed a weight advantage, his neonatal condition was judged good, and he was free from congenital malformations. R. was oriented in transverse presentation which led to delivery by internal version and breech extraction. His neonatal condition was judged poor. There was a velamentous insertion of this infant's cord and he possessed a cleft palate and cleft lip. Confirmation of zygosity was obtained through skin graft. At the time of intellectual evaluation, Q.'s IQ was 102, and R.'s IQ, 103. The IQ difference was one point.

Twin set 14: The twins S. and T. were concordant for all factors with the exception of weight. Both twins were delivered with cephalic presentation, no forceps were implemented, and neonatal condition was judged good. S. was the heavier infant. Confirmation of zygosity was obtained through serological examination. At the time of intellectual evaluation, S.'s IQ was 95, and T.'s IQ 117. The IQ difference was twenty-two points.

The view, expressed in the introduction to this paper, that "phenotypic variation may be assumed to express variation due to natal environmental differences" between identical twins seems inadequate to account for the discrepant relation between environmental factors and intrapair differences. If extrachromatozoic inheritance is presumed minimal and errors of measurement are ignored, two additional interpretations of the sources of intrapair differences seem plausible. The first interpretation stresses the role of complex hereditary interactions, and the second postulates a genetic indeterminance related, in part, to genetic heterogeneity.

## 1. Complex Interactions

The discrepant relation of environmental factors to twin differences suggests the probable importance of hereditary interactions in twin differences. However, as will be shown, the source of hereditary interactions is not confined to the twin set. Individual differences are the consequence of both environmental and hereditary influences:

$$(1) \qquad Vp_s = Vh_s + Ve_s + Vh_s \times e_s \ .$$

Where $Vp_s$ is the variance of the subject phenotype; $Vh_s$, variance due to heredity; $Ve_s$, variance due to natal environment; and $Vh_s \times e_s$, variance due to their interaction. This formula is typically applied in one or another version to estimate sources of individual variation in extrauterine environments. When applied to individuals in intrauterine environments, the environmental component may be partitioned into three subcomponents:

$$(2) \qquad e_s = pos_s + u_m + pos_s \times u_m \ .$$

Where $e_s$ is the environmental component; $pos_s$, the positional component, $u_m$, the maternal uterine component; and $pos_s \times u_m$, the interaction component. By substitution of equation (2) with (1):

$$(3) \qquad Vp_s = Vh_s + V(pos_s + u_m + pos_s \times u_m) + Vh_s\ (pos_s + u_m + pos \times u_m) \ .$$

The positional component implicates those sources of variation due to purely mechanical factors such as compressions of the umbilicus, fetal position,

placental site, etc. The maternal uterine component derives from maternal heredity, maternal environment, and their interaction:

$$u_m = h_m + e_m + h_m \times e_m \quad (4)$$

Then, by substitution of equation (4) with (3):

$$\begin{aligned} Vp_s = Vh_s + V\,[&pos_s + h_m + e_m + h_m \times e_m \\ &+ pos_s\,(h_m + e_m + h_m \times e_m)] \\ + Vh_s\,[&pos_s + h_m + e_m + h_m \times e_m \\ &+ pos_s\,(h_m + e_m + h_m \times e_m)] \end{aligned} \quad (5)$$

and, by multiplication:

$$\begin{aligned} Vp_s = Vh_s + Vpos + Vh_m + Ve_m + Vh_m \times e_m \\ + Vpos_s \times h_m + Vpos_s \times e_m + Vpos_s \times h_m \times e_m \\ + Vh_s \times pos_s + Vh_s \times h_m + Vh_s \times e_m + Vh_s \times h_m \\ \times e_m + Vh_s \times pos_s \times h_m + Vh_s \times pos_s \times e_m \\ + Vh_s \times pos_s \times h_m \times e_m . \end{aligned} \quad (6)$$

Thus, phenotypic differences of the subject are due to subject heredity, subject position, maternal heredity, maternal environment, the interactions of

maternal heredity with environment, subject position with maternal heredity, subject position with maternal environment, subject position with maternal heredity and environment, subject heredity with position, subject heredity with maternal heredity, subject heredity with maternal environment, subject heredity with maternal heredity and environment, subject heredity with position and maternal heredity, subject heredity with position and maternal environment, and subject heredity with position, maternal heredity and environment.

Equation (6) reveals the potential complexity of components which determine neonatal phenotypic differences. Traditional formulations of individual differences in terms of simple hereditary and environmental sources of variation tend to ignore or grossly oversimplify these determinants. The equation suggests the general importance of control for maternal and fetal heredity and, in the evaluation of intrapair twin differences, the specific importance of control for positional factors. A reliable statement about the direction of effect expected from natal manipulations for an individual case seems implausible in the absence of such control.

## 2. Genetic Indeterminance

An alternative, though not exclusive, interpretation of intrapair differences suggests that these differences reflect a genetically or environmentally conditioned variability of response. Specifically, a component of residual variation usually treated as error may derive from variation associated with environmental or hereditary sources. If

(7) $$h_1 = h_2$$

the heredity of twin 1 is the same as that of twin 2, and if

(8) $$e_1 = e_2$$

the environment for twin 1 is equivalent to that of twin 2, then any residual variation which is not error is indeterminate variation.

Just as phenotypic variation may covary with a large number of hereditary, environmental, and interaction components as in equation (6), so may indeterminate variation be associated with any one of these components. In the simplest case, with error of measure excluded, indeterminate variation may be partitioned into three sources,

(9) $$V_{tr} = V_{ih} + V_{ie} + V_{ih \times ie}$$

where $V_{tr}$ is the total residual variation; $V_{ih}$, indeterminate variation associated with heredity; $V_{ie}$, indeterminate variation associated with environment; and $V_{ih \times ie}$, indeterminate variation associated with their interaction. Equation (9) is identical in form to equation (1). The terms, however, are different. In equation (1) variance identifies systematic covariation; in equation (9) variance identifies systematic indeterminate variation.

Systematic indeterminate variation may be estimated through computation of residual variations for some factorial matrix. Such variation presumes that the pattern of residual variation within cells is nonrandomly distributed. In contrast, variation due to error of measurement presumes a random distribution about some mean value. Corrected indeterminate variation is the residual minus this value. In Table 6, corrected residual variation for two types of

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Insert Table 6 about here

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strains, $h_1$ and $h_2$, and for two environments, $e_1$ and $e_2$, is given for three hypothetical cases. In case 1, indeterminate variation is a function of heredity; in case 2, a function of environment; and, in case 3, a function of their interaction.

In general, indeterminate variation is equivalent to the difference between total variation, the sum of systematic covariation and variation due to error of measurement:

$$V_i = V_t - (V_s + V_{em}) . \tag{10}$$

This equation allows the expression of a "coefficient of indetermination" through computation of the ratio of indeterminate variation to total variation.

$$\delta = \frac{V_i}{V_t} . \tag{11}$$

To the extent that hereditary or environmental factors or their interactions covary with phenotypic differences in a systematic way, delta approaches zero. To this extent these factors fail to account for phenotypic differences and $V_i$ is nonzero, delta approaches unity. Analogously, the expression of a "coefficient of hereditary or environmental indeterminance" is the ratio of indeterminate variation associated with heredity or environment to total variation.

Systematic indeterminate variation of the type exemplified in Table 6 may derive either through incomplete control of those factors which account for differential variation or through some inherent instability associated with treatments, genotypes, or their interaction. If indeterminate variation

arises from incomplete control, then some factor levels implicate sources of variation other than those superficially identified with designated treatments or genotypes and, in principle, residual variation may be reduced to zero. On the other hand, if indeterminate variation follows from some inherent instability, then some factor levels by virtue of dynamic or structural characteristics are intrinsically more variable in outcome or expression and, in principle, residual variation, no matter how complete the control, remains.

Indeterminance associated with heredity may provide an example of a structurally predisposed instability. In all likelihood, the genome possesses considerable informational redundancy to determine phenotypic regularity (28). Redundancy possesses the same significance for biologic systems as it does for communication networks. The repetition of a message serves to reduce error. In information theory the source of error may be equated to noise, and in biophysical systems, to perturbations (random disturbances). In the average expected biological environment (whether natal or postnatal) perturbations may be presumed to be some nonzero value.

Genetic heterogeneity is an index of genetic mixture. If it is presumed that increased genetic heterogeneity decreases genetic redundancy, it follows that decreased genetic redundancy disposes to greater variability. The more variable the genome, the more variable potential development.

This conclusion leads to the expectation that intrapair twin differences are, in part, a function of the degree of genetic heterogeneity of the twin set. A crude, but useful, measure of heterogeneity is the number of national origins in the parental background (3). Mothers in the present study and two sets with previous special education were contacted and the national origins of the twin set's grandparents ($P_2$ generation) requested. Eighteen mothers

replied. Of this group, four mothers did not know the national origin of the twin set's maternal and paternal grandparents. The reduced sample size was fourteen. Twin sets were classified as either low heterogeneous (1-2 countries of origin for the $P_2$ generation) or high heterogeneous (3-4 countries of origin for the $P_2$ generation). Mean difference scores and variations were calculated for birth weight and intelligence (Table 7).

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Insert Table 7 about here
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Although t tests for difference scores for birth weight and intelligence between high and low heterogeneous groups were not significant, the direction of effect was consistent with expectation. Difference scores and their variation increased with genetic heterogeneity. If, as implicated, instabilities of phenotypic response derive from genetic predisposition, those studies which estimate environmental effect by reference to intraindividual twin differences may require qualification (25). Some coefficient of genetic indetermination may be a characteristic property of various strain and racial groups.

## F. Summary

Although psychological studies of natal factors by the method of co-twin control largely have concerned the relation of intrapair birth weight difference to intellectual difference, many natal factors other than birth weight are subject to evaluation by the co-twin method. Natal co-twin studies require the identification of specific pre- or paranatal, environmental or organismic factors which differentially affect members of the twin set. The majority of these factors operate through the increase or decrease of maternal capacity, maternal

load, or maternal efficiency. Since the increased demands of twin pregnancy increase maternal load, which may exceed maternal capacity to provide adequate oxygen, nutrients, and metabolite elimination, the results of twin studies must be interpreted with caution.

Natal histories and intellectual examinations were obtained for a total of 16 sets of identical twins between the ages of 10 to 90 months. Correlational analyses of intellectual differences and intrapair differences for birth order, birth weight, presentation, neonatal Apgar, and use of forceps were nonsignificant. The failure to replicate earlier investigations which suggested an intellectual advantage for the heavier twin prompted the reevaluation of the primary data from these studies. No consistent relationship between weight advantage and intellectual difference was demonstrated. These results appear inconsistent with the hypotheses of intrauterine, circulatory, or nutritional insufficiency which suggest some correspondence between weight and intellectual advantage within sets.

In contrast to the negative results for intrapair analyses, interpair analyses for general prenatal factors were largely in the expected direction. Neonatal maturity and diagnostic X-ray were significantly inversely related to midtwin intelligence while chronological age at the time of examination was significantly positively related. The former factors are measures of maternal load and imply that prematurity among twins may provide an adaptation to limited maternal capacity. Correspondingly, the intellectual "catch-up" growth evidenced by identical twins suggests differential injury to lower brain centers associated with decreased maternal efficiency. Thus, while intellectual differences between twin sets were related to general prenatal factors, differences within sets were unrelated to specific factors. That is, with genetic control, intrapair intellectual differences were independent of intrapair natal

differences. This result suggested the reevaluation of traditional models of neonatal variation. Two alternative, but nonexclusive, models were formulated.

The first model stresses the role of complex maternal-fetal interactions which determine phenotypic variation. Intrapair intellectual differences are not a simple function of intrapair natal differences. The magnitude and direction of effect depend upon the individual maternal-fetal genome.

The second model suggests a "genetic indetermination" related to the genetic heterogeneity of the twin set. When genetic redundancy is reduced through outcrossing, the probability of divergent development is enhanced. A measure of outcrossing was obtained for the present sample and, although the results were nonsignificant, the magnitude and variability of intellectual and weight difference increased with genetic heterogeneity.

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Footnotes

[1]Sections of this paper were presented at the second annual Behavior Genetics conference at Boulder, Colorado and at a University of North Carolina Medical School, Grand Rounds Colloquium.

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Table 1

Typology of Selected Natal Factors

| | Prenatal | | Paranatal | |
|---|---|---|---|---|
| | Environmental | Organismic | Environmental | Organismic |
| Specific | Palpation<br>Transplacental transfusions<br>Mechanical compressions of umbilicus<br>Fetal position | Hydramnios<br>Oligamnios | Forceps implementation<br>Period of umbilical separation | Neonatal Apgar<br>Birth weight<br>Birth order<br>Presentation |
| General | Medications<br>Drugs<br>Exposure to ionizing radiation<br>Maternal nutrition | Maternal age<br>Maternal disease<br>Maternal dysfunctions<br>Maternal sensitization<br>Nutrition | Anesthetic<br>Analgesic | Pelvic inadequacy<br>Length of labor |

Table 2

Representative Natal Factors Related to Maternal Capacity, Load, and Efficiency

| Maternal Capacity | Maternal Load | Maternal Efficiency |
|---|---|---|
| Maternal weight | Prescriptions | Eclampsias |
| Maternal height | Ionizing radiation | Toxemias |
| Pelvic girth | Fetal maturity | Oedema |
| Nutrition | Fetal number | Miscarriages |
| Maternal age | Fetal dysfunctions | Parity |

Table 3

Intrapair Natal and Intellectual Differences

| Factor | n | Mean Intrapair Factor Difference | Mean Intrapair IQ Difference | $r_{\text{Factor Difference x IQ Difference}}$ | p* |
|---|---|---|---|---|---|
| Birth order | 16 | 1.00 | 3.82 | .41 | n.s. |
| Birth weight | 16 | 269.25 | 0.75 | .00 | n.s. |
| Presentation | 6 | .44 | 1.9 | .11 | n.s. |
| Neonatal Apgar | 4 | .25 | 3.80 | -.25 | n.s. |
| Forceps | 2 | .13 | 3.50 | -.15 | n.s. |

*2-tailed test

Table 4

Intrapair Birth Weight and Intellectual Differences

by Study

| Study | n | Mean Intrapair Weight Difference | Mean Intrapair IQ Difference | $r_{\text{Weight Difference x IQ Difference}}$ | p* |
|---|---|---|---|---|---|
| Babson | 9 | 845 | 6.5 | -.24 | n.s. |
| Churchill | 13 | 220 | 3.0 | -.30 | n.s. |
| Kaelber and Pugh | 42 | 294 | 2.1 | .28 | n.s. |
| Scarr | 25 | 334 | 8.9 | .01 | n.s. |
| Willerman and Churchill | 27 | 270 | 5.3 | .01 | n.s. |

*2-tailed

Table 5

Interpair Natal and Intellectual Differences

| General Factors | Mean Interpair Factor Score | Sigma | $r_{\text{Mean Factor Score x Midtwin IQ}}$ | p* |
|---|---|---|---|---|
| Prenatal Organismic Factors | | | | |
| Maternal Age | 26.56 | 5.78 | -.30 | n.s. |
| Miscarriages | 0.56 | 1.26 | -.10 | n.s. |
| Maternal Parity | 1.44 | 1.41 | .02 | n.s. |
| Maternal Weight | 61.44 | 17.73 | .26 | n.s. |
| Weight Gain | 9.19 | 4.64 | -.24 | n.s. |
| Maternal Dysfunction | .75 | .66 | -.19 | n.s. |
| Maternal Oedema | 1.06 | 1.29 | .00 | n.s. |
| Prenatal Environmental Factors | | | | |
| X-ray | .69 | .48 | -.43 | <.05 |
| Prescriptions | 1.31 | 1.01 | -.13 | n.s. |
| Paranatal Organismic Factors | | | | |
| Neonatal Maturity | 4.06 | 1.34 | -.42 | <.05 |
| Length of Labor | 1.88 | .47 | .08 | n.s. |
| Mean Apgar | 2.69 | .54 | .06 | n.s. |
| Mean Birth Weight | 2.41 | .47 | -.36 | n.s. |
| Paranatal Environmental Factors | | | | |
| Anesthetic | 2.38 | 1.02 | .08 | n.s. |
| Umbilical Separation | 1.63 | .50 | -.17 | n.s. |
| Nonnatal Factors | | | | |
| Sex | .68 | .49 | -.08 | n.s. |
| Chronological Age | 52.69 | 27.38 | .78 | <.01 |

*One-tailed tests were applied to natal factors for which a direction of effect was expected from the maternal capacity-load-efficiency model.

Table 6

Systematic Residual Variation for Three Hypothetical Cases

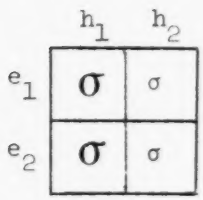
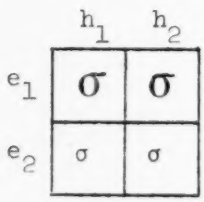
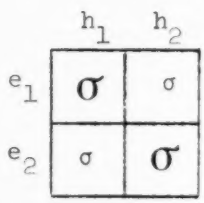
| Case 1 | Case 2 | Case 3 |
|---|---|---|
|  |  |  |

Table 7

Mean Intrapair IQ and Birth Weight Differences for

High and Low Heterogeneous Groups

| | | Intrapair IQ Difference | |
|---|---|---|---|
| | N | X | σ |
| Low Heterogeneous | 7 | 6.9 | 3.2 |
| High Heterogeneous | 7 | 11.1 | 9.7 |
| | | Intrapair Birth Weight Difference | |
| Low Heterogeneous | 7 | 255.15 | 244.42 |
| High Heterogeneous | 7 | 340.19 | 413.42 |